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The effects of bromazepam over the temporo-parietal areas during the performance of a visuomotor task: A qEEG study

Fernanda Araújo[a,k], Sergio Machado[a,f,i], Flávia Paes[i,j], Marlo Cunha[a,f,g], Henning Budde[h], Mauricio Cagy[c], Luis F. Basile[d,e], Oscar Arias-Carrión[l], Bruna Velasques[a,f,k,m,*], Roberto Piedade[a], Pedro Ribeiro[a,b,f]

[a] Brain Mapping and Sensory Motor Integration, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Brazil
[b] School of Physical Education, Bioscience Department (EEFD/UFRJ), Brazil
[c] Division of Epidemiology and Biostatistics, Institute of Community Health, Federal Fluminense University (UFF), Rio de Janeiro, Brazil
[d] Division of Neurosurgery, University of São Paulo Medical School, Brazil
[e] Laboratory of Psychophysiology, Faculty of Psychology and Phonology, Methodist University of São Paulo (UMESP), Brazil
[f] Institute of Applied Neuroscience (INA), Rio de Janeiro, Brazil
[g] School of Physical Education, Laboratory of Motor Behavior, Federal University of Vale do São Francisco (UNIVASF) – Pernambuco, Brazil
[h] Department of Movement and Training Science, Institute of Sports Science, Humboldt University zu Berlin, Germany
[i] Panic & Respiration Laboratory, Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[j] Faculty of Psychology, Brazilian Institute of Medicine and Rehabilitation (IBMR), Rio de Janeiro, Brazil
[k] Neurophysiology and Neuropsychology of Attention, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Brazil
[l] Department of Neurology, Phillips University Marburg, Marburg, Germany
[m] Neuromuscular Research Laboratory, National Institute of Traumatology and Orthopaedics (NITO), Rio de Janeiro, Brazil

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ABSTRACT

This study investigated the effects of bromazepam on qEEG when 14 healthy subjects were asked to perform a visuomotor task (i.e., motor vehicle driving task). The subjects were exposed to two experimental conditions: the placebo (PL) and 6 mg of bromazepam (Br 6 mg), following a randomized, double-blind design on different days. Specifically, we observe absolute power extracted from qEEG data for theta band. We expected to see a decrease in absolute theta power in the temporal and parietal areas due to the influence of bromazepam for the experimental group when compared with the placebo group. We found a main effect for the condition factor for electrodes T3, T4, P3 and P4. We also observed a main effect for the period factor for electrodes P3 and P4. We observed that the ingestion of 6 mg of bromazepam induces different patterns in theta power at the temporal and parietal sites. We concluded that 6 mg of bromazepam was an important factor in the fluctuation of the activities in the temporal and parietal areas. We then hypothesize about the specific role of this drug during the execution of a visuomotor task and within the sensorimotor integration process.

A relevant issue in cognitive neuroscience is the sensitivity of EEG activity to detect changes produced by different substances, such as bromazepam, methylphenidate and modafinil [8,25,27]. Changes in qEEG variables can be used to explore the mechanisms of drug effects in order to investigate sensorimotor integration and cognitive processes [7,8,17]. Benzodiazepine, particularly bromazepam, is the most prescribed and abused pharmacologic group (worldwide) for the management of anxiety and insomnia [20,4]. Benzodiazepines have been used to understand how the cerebral cortex works during the performance of sensorimotor integration tasks. However, this is still not entirely understood. For instance, some studies have shown that bromazepam may impair psychomotor capacity when individuals are submitted to neuropsychological testing, such as memory, attention, reaction time, and vigilance performance [5,4]. It has been suggested that the impairment caused by bromazepam takes place in the early stages of sensory-motor integration (i.e., stimulus identification), thereby undermining the entire system of identification of the stimulus to the execution of motor task [7,11]. This study is justified by the increase in the prescription of benzodiazepines and their use in addition there is a lack of studies on the effects of this drug on sensory-motor integration in healthy subjects.

We used a paradigm similar to the S1–S2 paradigm to investigate sensorimotor integration during a visuomotor task. The paradigm involves a warning stimulus (S1) and an imperative

* Corresponding author at: Rua Paula Brito 350/1102, Andaraí, CEP 20541-190, Rio de Janeiro, RJ, Brazil. Tel.: +55 21 25714134.
E-mail address: bruna_velasques@yahoo.com.br (B. Velasques).

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stimulus (S2), however, we did not analyze the contingent negative variation (CNV). One of the most influential neurophysiological theories about the S1–S2 paradigm is that it readies the cortex for processing the next stimulus and response, i.e., S2 stimulus, due to an advisory signal, i.e., S1 stimulus [11]. According to those principles and considering the features of each area, we expected to see the effects of bromazepam in the left and right temporal and parietal cortices. Several studies demonstrated that the temporal areas are involved in the transmission of multimodal sensory information, i.e., neurons in these areas are sensible to stimuli of different modalities, enabling multisensory interactions [1,9,17]. Moreover, the parietal lobe integrates sensory information from several channels [9,21].

Thus, our objective is to investigate the effects of bromazepam on qEEG when subjects were submitted to a visuomotor task (i.e., motor vehicle driving task). Specifically, we observed absolute power extracted from qEEG data for theta band. The increase of theta power has been related to increases in mental effort during the encoding of sensory information, attention demand, higher task difficulty and increasing cognitive load [18,19,31]. We expected to see a decrease in absolute power for the experimental group when compared with the placebo group in the left and right temporal and parietal areas due to the drug's influence. Thus, the assessment of qEEG may unveil how the temporal and parietal areas participate in the organization and integration of sensory information, in other words, the performance of cognitive operations and the achievement of motor control during the performance of multiple complex tasks under the effect of bromazepam.

The sample was composed of 14 healthy subjects (nine male and five female; mean age: 32.5, SD: 9.5). The inclusion criteria included the absence of mental or physical impairments and no history of psychoactive or psychotropic substance use (screened by a previous anamnesis and a clinical examination). All subjects were also right handed, according to the Edinburgh inventory [24]. Moreover, they had no less than 6–8 h of sleep prior to the experiment and no previous experience with the task. All subjects signed a consent form and were aware of the experimental protocol. The experiment was approved by the Ethics Committee at the Federal University of Rio de Janeiro according to the principles of Helsinki Declaration [13].

The task was performed in a sound and light-attenuated room, to minimize sensory interference. Each subject was exposed to both the experimental conditions: the placebo (PL) and 6 mg of bromazepam (Br 6 mg), following a randomized, double-blind design on different days. (Thus, each subject was exposed to one condition on the first day and the other condition on the second day. The subjects performed the conditions in one week interval.) After the capsule ingestion, subjects remained at rest for 1 h [23]. Then, a computer monitor (Sansung-SyncMaster 550v) was positioned in front of the subjects as they sat on a comfortable chair to minimize muscular artifacts, while electroencephalography (EEG) data were recorded before, during and after the motor task execution.

Subjects were asked to perform a visuomotor task (S1–S2 paradigm – motor vehicle driving task). The task was controlled and synchronized with the qEEG recording by the software Car Acquisition (Delphi 5.0). The visuomotor task consisted of driving a car at a slow and fixed speed. Subjects were instructed to pay attention to curves and to respond as quickly possible when an action command appeared. The proper response was to press the anterior button of the *joystick* (Model Quick Shot-Crystal CS4281) which was fixed onto a support attached under the chair, to avoid hand instability. Each subject was submitted to 50 trials under each experimental condition. The task was composed of 0.5 ms periods, before and after the appearance of each stimulus (i.e., pre-S1, post-S1, pre-S2 and post-S2). The warning stimulus (S1 – yellow square) and the action stimulus or command (S2 – red triangle) appeared at a fixed interval of 2.5 s (intra-stimulus interval). However, the interval between the re-appearance of S2 and S1 varied randomly from 2.5 and 15 s (inter-stimulus interval) to avoid providing cues for the occurrence of S1.

The International 10/20 EEG System for electrodes [16] was used with the 20-channel EEG Braintech-3000 system (EMSA-Medical Instruments, Brazil). The 20 electrodes were arranged in a nylon cap (ElectroCap Inc., Fairfax, VA, USA) yielding monopolar derivations referred to linked earlobes. In addition, two 9-mm diameter electrodes were attached above and on the external corner of the right eye, in a bipolar electrode montage, for the monitoring of eye-movement (EOG) artifacts. Impedance of EEG and EOG electrodes was kept between 5 and 10 kΩ. The amplitude of the data acquired totaled less than 100 μV. The EEG signal was amplified with a gain of 22,000, analogically filtered between 0.01 Hz (high-pass) and 100 Hz (low-pass), and sampled at 240 Hz. The software Car Acquisition (Delphi 5.0) at the Brain Mapping and Sensory Motor Integration Lab was employed with the following digital filters: notch (60 Hz), high-pass of 0.3 Hz and low-pass of 25 Hz.

To quantify reference-free data, a visual inspection and independent component analysis (ICA) were applied to remove as many sources of artifacts produced by the task as possible [15]. Data from individual electrodes exhibiting loss of contact with the scalp or high impedances (>10 kΩ) were deleted and data from single-trial epochs exhibiting excessive movement artifacts (±100 μV) were also deleted. ICA was then applied to identify and remove any remaining artifacts after the initial visual inspection. ICA is an information maximization algorithm that is derived from spatial filters through the blind source separation of EEG signals into temporally independent and spatially fixed components. Independent components resembling eye-blink or muscle artifacts were removed and the remaining components were then back-projected onto the scalp electrodes by multiplying the input data by the inverse matrix of the spatial filter coefficients derived from ICA using established procedures. The ICA-filtered data were then re-inspected for residual artifacts using the same rejection criteria described above. Then, a classic estimator was applied for the power spectral density (PSD), or directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB 5.3 (Matworks, Inc.). Quantitative EEG parameters were extracted from 2 s periods (the selected epoch started 0.5 ms before and after the appearance of each stimulus, i.e., S1 and S2, respectively), for consecutive (non-overlapping) artifact-free, 2-s EEG epochs (spectral resolution: 0.25 Hz), with rectangular windowing. In this manner, based on artifact-free EEG epochs, the threshold was defined by mean plus three standard deviations. Epochs with a total power higher than this threshold were not integrated into the analysis.

We analyzed the anterior-temporal (T3 and T4) and the parietal (P3 and P4) areas. The first one plays an important role in supplying multimodal sensory information for the performance of voluntary movements and sensorimotor integration [12]. The parietal areas are functionally related to the integration of sensory information from different modalities [21], manipulation of objects, attention and visuospatial processing [2,6]. The theta band (4.5–8 Hz), was chosen due to its association with cognitive functions such as stimuli encoding [3], attention mechanisms [29] and information transmission [19].

The qEEG absolute power values were $\log_{10}$-transformed by SPSS software (version 16.0) to approximate a normal distribution. A two-way ANOVA was used to analyze between the conditions (i.e., PL × Br 6 mg), and between the periods (i.e., pre-S1, post-S1, pre-S2, post-S2) for each electrode (i.e., T3, T4, P3, P4). A Scheffé test was applied to analyze significant differences between the periods ($p < 0.05$).